Melanotic neuroectodermal tumour of infancy: A clinicopathological study with emphasis on histopathology and IHC

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Abstract

Aims: To explore clinical, Histopathological and IHC features of MNTI with systematic literature review.

Settings and Design: Hospital based retrospective study.

Methods and Materials: Data of all cases of MNTI diagnosed over a period of seven years i.e. from 2008 to 2015 was retrieved. H&E sections and IHC sections were studied. Strict histological and recently updated criteria were applied and patients with a confirmed diagnosis of MNTI were included in the study. A systematic literature review was conducted by searching the PubMed and National Centre for Biotechnology Information database.

Statistical analysis used: Microsoft Excel 2010

Results: Present case series is 19th in the English literature and 2nd in the Indian literature. Mean age of presentation is 5 months. Average duration of symptoms is 2.1 months. Male preponderance was found i.e. M:F ratio of 2:1. Histopathology and if necessary, followed by IHC is required for the confinement of diagnosis. No histological marker can predict its behaviour.

Conclusions: A number of known pathologic entities can present at infancy but confirmation of the diagnosis requires histopathological examination and IHC, if necessary. Any unusual growth in infants that appear inconsistent with normal variation and reported history should be referred in time to a pathologist for assessment and diagnosis. A diagnosis of MNTI should be suspected in any tumour in an infant with round cell morphology and a careful search for large melanin containing epithelial cells will help in accurate diagnosis.

Keywords: Melanotic neuroectodermal tumour of infancy, Round cell tumour, Melanin pigment, Melanoticprogonoma, Retinal anlage tumour

Key Messages: A diagnosis of MNTI should be suspected in any tumour in an infant with round cell morphology and a careful search for large melanin containing epithelial cells will help in accurate diagnosis.

Introduction

Melanotic neuroectodermal tumour of infancy (MNTI), described first in 1918 by Krompecher, is a rare, benign pigmented neoplasm of neural crest origin occurring in infants.¹ The majority of these tumours (90%) arise in the head and neck region, mostly affecting anterior maxilla.² MNTI is a locally aggressive, rapidly growing tumour.³ Rate of recurrence is 20% within six months.⁴ Because of its rapid growth potential there can be a misdiagnosis of malignancy, though the incidence of malignancy development is rare.⁵ Clinical and radiological findings may suggest a diagnosis of MNTI, but histopathological examination and if necessary, followed by IHC is required for the accurate diagnosis.

We hereby report three cases of MNTI and discuss the clinical, histomorphological and IHC features of this rare tumour with systematic review of literature. As per author’s knowledge this is the 19th case series in the English literature and second in the Indian literature.

Materials and Methods

This retrospective study comprises three cases of MNTI diagnosed over a period of seven years (from 2008 to 2015). All cases were documented; detailed clinical information was recorded from the case sheets. This included age and sex of the patients, duration of illness and site of biopsy. All three tumours were resected or biopsied, and pathological examination was performed on representative fixed-tissue samples embedded in paraffin and stained with H&E.

Haematoxylin & eosin stained sections were studied and the following histological features were evaluated:

1. Pattern of growth
2. Morphology of cells and their relative preponderance
3. Presence of melanin pigment

Subsequently, IHC was done. The following antibodies were used according to histomorphological features: Synaptophysin, GFAP, CK, EMA, HMB-45, Vimentin, NSE, Desmin, Chromogranin & S100. Strict histological and recently updated criteria were applied and patients with a confirmed diagnosis of MNTI were included in the study.

Systematic Review

A systematic literature review was conducted by searching the PubMed and National Centre for Biotechnology Information database using the keyword search term melanotic neuroectodermal tumour of infancy case series and the Medical Subject Heading term neuroectodermal tumour, melanotic. All case series of MNTI cases published hitherto were included. Excluded were reports published in a language other than English and without an English-language abstract. This yielded a total of...
18 publications, which included 97 cases. (Table 1) This analysis included gender, age at diagnosis and tumour site.

Ethics: Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000

Results
Between 2008 to 2017, three cases of MNTI were diagnosed. The clinical characteristics of the three cases are summarized in Table 2. On systematic review, it was found that the present case series is nineteenth in the English literature and second in the Indian literature. Also, in “case two” the lesion was present at femur which happens to be the seventh case to be reported in the world literature. The mean age of presentation was five months. There was a male preponderance. Average duration of symptoms was 2.1 months. Most predominant symptom was gradually increasing swelling.

FNAC could be done only in the last case. Cellular cytosmears showed disperse pattern, predominantly composed of round cells which outnumbered large epithelial cells. Among the dual population of cells, the round cells showed occasional rosettes. While, the large epithelial cells formed small cohesive clusters with brown pigment. A cytomorphological diagnosis of Round cell tumour was made & possibilities of Rhabdomyosarcoma, Neuroblastoma, MNTI and NHL were considered. The presence of melanin containing large cells which were found on a careful search is the key diagnostic feature of MNTI. Hence a final FNAC diagnosis of Round cell tumour suggestive of MNTI was given.

Histopathological features of all the three cases are summarized in the table below. (Table 3)

IHC features of all the cases are summarised in the table below. (Table 4)

Table 1: Previously reported case series of MNTI

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Study</th>
<th>Number of cases</th>
<th>Mean age (months)</th>
<th>M:F ratio</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allen M.S. et al[7] 1968</td>
<td>3</td>
<td>4.6</td>
<td>02:01</td>
<td>Maxilla-1, Mandible-1, Skull-1</td>
</tr>
<tr>
<td>4</td>
<td>Mirich et al[10] 1990</td>
<td>5</td>
<td>9</td>
<td>04:01</td>
<td>Maxilla-4, Calvaria-1</td>
</tr>
<tr>
<td>7</td>
<td>Yu et al[12] 1992</td>
<td>2</td>
<td>20</td>
<td>all males</td>
<td>Skull-2, brain-1</td>
</tr>
<tr>
<td>9</td>
<td>Demas et al[14] 1992</td>
<td>2</td>
<td>3.5</td>
<td>all females</td>
<td>Maxilla-2</td>
</tr>
<tr>
<td>10</td>
<td>Kapadia et al[15] 1993</td>
<td>20</td>
<td>4.8</td>
<td>0.17:1</td>
<td>Maxilla-13, Mandible-3, Brain-1, Dura-2 &amp; skull-1</td>
</tr>
<tr>
<td>11</td>
<td>Nelson et al[16] 1995</td>
<td>2</td>
<td>6.5</td>
<td>all males</td>
<td>Maxilla-1, Mandible-1</td>
</tr>
<tr>
<td>12</td>
<td>El Saggat et al[17] 1998</td>
<td>2</td>
<td>5.5</td>
<td>all males</td>
<td>Maxilla-2</td>
</tr>
<tr>
<td>13</td>
<td>Khoddami et al[18] 1998</td>
<td>3</td>
<td>5.3</td>
<td>02:01</td>
<td>Maxilla-3</td>
</tr>
<tr>
<td>14</td>
<td>de Souza et al[18] 1999</td>
<td>3</td>
<td>7.5</td>
<td>all females</td>
<td>Maxilla-3</td>
</tr>
<tr>
<td>16</td>
<td>Barett A.W. et al 2002</td>
<td>8</td>
<td>5.92</td>
<td>07:01</td>
<td>Maxilla-7, mandible-1</td>
</tr>
<tr>
<td>17</td>
<td>Chaudhary A. et al 2009</td>
<td>18</td>
<td>4.2</td>
<td>02:01</td>
<td>Maxilla-18</td>
</tr>
<tr>
<td>18</td>
<td>Butt F.M.A. et al 2009</td>
<td>3</td>
<td>10.5</td>
<td>02:01</td>
<td>Maxilla-3</td>
</tr>
</tbody>
</table>

Table 2: clinical features of three cases of MNTI

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (year of diagnosis)</th>
<th>Sex</th>
<th>Duration</th>
<th>Site</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 months (2008)</td>
<td>Female</td>
<td>2 months</td>
<td>Left upper gingival (Fig. 1a)</td>
<td>Mass extruding from the mouth, No airway or pharyngeal compression</td>
</tr>
<tr>
<td>2</td>
<td>4 months (2012)</td>
<td>Male</td>
<td>15 days</td>
<td>Left lower femur</td>
<td>Swelling left lower thigh</td>
</tr>
<tr>
<td>3</td>
<td>4 months (2015)</td>
<td>Male</td>
<td>Since birth</td>
<td>Right upper gingiva &amp; maxillary region (Fig. 1b)</td>
<td>Gradually increasing maxillary swelling &amp; difficulty in taking feeds due to obstruction</td>
</tr>
</tbody>
</table>
Table 3: Histomorphological features of the cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Procedure done</th>
<th>Gross features</th>
<th>Microscopy</th>
</tr>
</thead>
</table>
| 1.       | Excisional biopsy | • Dark brown, firm mass.  
• Measured 5.5 X 4.9 X 4.7 cm  
• Overlying mucosa was ulcerated and showed brownish discoloration. | • Polypoidal mass showing predominantly large cuboidal  
• To polygonal cells, some containing melanin pigment  
• Arranged in pseudoalveolar pattern. (Fig.3b)  
• Admixed round cells in the fibrocollagenous stroma.  
• Large polygonal epithelial cells outnumbered round cells. (Fig.3a) |
| 2.       | Needle biopsy | Multiple light brown bits, largest measured 2x0.2x0.2 cm | • Round cell tumour.  
• Foci of polygonal cells with intracytoplasmic brownish pigment. (Fig.3c)  
• Large polygonal epithelial cells were equal in number as the round cells. (Fig. 3d) |
| 3.       | Wide local excision of mass with partial maxillectomy | • Polypoidal mass with normal overlying mucosa  
• Measured 4.5X4X3.7 cm  
• C/S: solid, encapsulated, grey white mass beneath the mucosa with brownish black discoloration.(Fig.4a) | • Biphasic pattern: Small and large cells  
• Small cells – small, round, hyperchromatic nuclei with  
scanty eosinophilic cytoplasm, mimicking neuroblast  
• Large cells - cuboidal epithelial cells with large round to  
oval vesicular nuclei with abundant eosinophilic cytoplasm arranged in pseudoalveolar or tubular patterns  
• Few cells show brown intracellular melanin granules  
• Round cells outnumbered large polyhedral epithelial cells. (Fig. 4 b-f) |

Table 4: IHC profile of the three cases of MNTI (*Large polygonal epithelial cells)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Type of cells</th>
<th>Synaptophysin</th>
<th>GFAP</th>
<th>CK</th>
<th>EMA</th>
<th>HMB45</th>
<th>Vimentin</th>
<th>NSE</th>
<th>Desmin</th>
<th>Chromogranin</th>
<th>S100</th>
<th>Mic-2</th>
<th>LCA</th>
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</thead>
<tbody>
<tr>
<td>(Fig. 5 &amp; 6)</td>
<td>LPEC*</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>(Fig. 5 &amp; 6)</td>
<td>Round cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(Fig. 5 &amp; 6)</td>
<td>LPEC*</td>
<td>-</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(Fig. 5 &amp; 6)</td>
<td>Round cells</td>
<td>+</td>
<td>ND</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>(Fig. 5 &amp; 6)</td>
<td>LPEC*</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td></td>
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<tr>
<td>(Fig. 5 &amp; 6)</td>
<td>Round cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td></td>
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</table>

Fig. 1: Clinical photographs of a) Case 1, b) Case 3
Fig. 2: From case 3, H & E stained cellular cytosmears showing a) A cluster of large epithelial cells showing melanin pigment (inset showing higher magnification for the same) with many round cells in the background, b) Round cells arranged in rosette (inset showing higher magnification for the same) Magnification: 10X

Fig. 3: Case 1, H&E stained sections showing: a) Large epithelial cells which outnumber small round cells in the background, b) Large epithelial cells with melanin pigment with few round cells in the background. Case 2, H&E stained sections showing: c) Large cells with focal melanin pigment admixed with equal proportion of small round cells, d) Round cells and Large epithelial cells almost in equal proportion. Magnification: a) & d) – 10X, b) & c) – 40X
Fig. 4: a) Gross picture of the tumour in case 3, showing a submucosal tumour with brown-black discoloration on cut surface. H&E stained sections showing b) Well circumscribed submucosal tumour with dual population of cells, c) Tumour cells infiltrating bony trabeculae d) Round cells outnumbering large epithelial cells, e) Round cells with admixed large cells, f) Clusters of large epithelial cells containing pigment. Magnification: b) to d) – 10 X, e) to f) - 40 X
Fig. 5: Large polygonal epithelial cells were positive while small round cells were negative for IHC markers- a) CK, b) EMA, c) HMB45. Small round cells were positive while large polygonal epithelial cells were negative for IHC markers- d) NSE, e) Synaptophysin & d) Chromogranin. Magnification: a) to c) - 40X, d) to f) -10X"
Discussion

MNTI is defined as a locally aggressive, rapidly growing tumour consisting of biphasic population of small neuroblast-like and larger melanin-producing epithelial cells. The tumour has various synonyms in the English literature, such as Melanotic Progroma and Retinal anlage tumour, both these synonyms are obsolete and not recommended according to WHO 2017 Classification of Head & Neck Tumours. This variable nomenclature reflects the uncertainty about the tumour’s origin, which prevailed for half a century, until Borello and Gorlin proposed the neural crest origin of this tumour in 1966. This was based on the fact that a subset of these patients excreted large amounts of vanillyl mandelic acid (VMA) which is associated with other neuroendocrine tumours.

Neural crest cells are multipotent embryonic cells that ultimately differentiate into various structures, including the odontogenic ectomesenchyme, melanocytes, and neural ganglia. These cells display mesodermal and ectodermal morphologic features at different stages of their ontogeny, explaining the difficulty in deciphering the embryologic origin of these tumours and possibly explaining the biphasic cellular phenotype such tumours display.

More than 90% cases are infants, with a median age of five months. Though rare, some cases are reported in adults also. There are 18 case-series of MNTI in the English literature. Since the first description in 1918, 472 cases were reported until last extensive review in 2015 by Rachidi et al.

These studies are summarised in the table below. (Table 1) The mean age of presentation in the previous case series ranged from 2.25 to 16.6 months. The mean age in our case series is 5 months. Currently, age at manifestation is considered to be a strong prognostic indicator of MNTI. Infants who manifested within the first 2 months of birth were associated with a high risk of recurrence which generally occurred within 6 months from treatment. In contrast, manifestation from 2.5 to 4 months was associated with an intermediate risk and manifestation after 4.5 months of age had a minimal risk of recurrence. Also, Rachidi et al. found that an older age correlated statistically with disease-free survival.

Though no gender predilection was reported by Stowens and Lim (1974), but a male to female ratio of 1.48 was given by Kruse-Losler in 2006 after a review of 140 cases. Also in a review by Rachidi et al which considered all the reported cases of MNTI from year 1918 to 2013, a male to female ration of 1.43 was given. In majority of the previous case series there is male predominance. According to WHO 2017 Classification of Tumours of Head and Neck, there is a slight male predilection. In our case series too there is male predominance (Male: Female ratio of 2:1).

More than 90% of the cases occur in the craniofacial regions, most commonly in the maxilla (>60%), followed by skull, mandible (6%) and brain. Outside Head and neck, the most common sites are the testis and epididymis. Rare cases occur in the ovary, uterus, mediastinum, scalpula, and bones and soft tissue of the extremities. In the previously reported case series as well as reviews the most common site is maxilla. In our study the most common site is Maxilla. Johnson R.E. first reported MNTI at femur. As per authors’ knowledge there are only six cases of MNTI of femur in the English literature.

The MNTI clinically presents as a rapidly growing, painless, expansile, unencapsulated partly pigmented mass, typically in the maxillary region. The pigmentation cannot be always observed through the overlying tissue. It tends to occur as a single lesion. However, multiple lesions have also been reported. Lesion was solitary in all the cases of the present case series. Also, the non-ulcerative bluish-black gingival mass is often confused with an eruption cyst. It might appear malignant due to its rapid growth. MNTI usually carries one of the primary central incisors outward with it, if in the maxilla. It does not carry both central incisors because the tumour arises from one side of midline. The lesion is destructive and radiographs show local irregular resorption of bone and displacement of tooth buds.
The only radiopaque components present are those of the developing teeth buds. In most of the studies including the present one the clinical histories are very similar and consisted of rapidly enlarging mass, most occurring in the first six months of life and discovered by parents.

In addition to the typical clinical presentation, the cytomorphology is also distinctive showing round cells with large polygonal cells in varying proportion. Usually a diagnosis of malignant round cell tumour is made with a differential diagnosis of Rhabdomyosarcoma, Neuroblastoma and NHL. However presence of large polygonal cells containing melanin pigment is clue to the diagnosis of MNTI. Typical cytomorphological diagnosis was done in only one of the three cases of this case series.

Microscopically, the two principle components of this tumour are the cuboidal pigment containing cells and the neuroglia like cells, both the type of cells are known derivatives of neuroectoderm. The cell population consisting of cuboidal epithelial cells have open vesicular nuclei clustered in alveolar or tubular patterns. These cells typically have abundant brown intracellular melanin granules. The second type of cells is small, round and dark with hyperchromatic nuclei and minimal cytoplasm. These cells vanillyl mandelic acid (VMA). These cells aggregate in loose nests or islands against the back ground of fibrovascular tissue. The tumour may show infiltration into adjacent bone as seen in the second case of our case series. (Fig. 4c) Fontana stain can be used to highlight the melanin. IHC help in confirmation of the diagnosis in doubtful cases lacking typical histologic features.

On IHC, the large epithelial cells are positive for cytokeratin, EMA, HMB 45, synaptophysin, vimentin and neuron specific enolase. The smaller cells are positive for neuron specific enolase, glial fibrillary acidic protein and synaptophysin. S-100 protein is usually non-reactive. In our case series too there was similar polyphenotypic expression of neural, epithelial and melanotic markers.

The incidence of malignancy is rare and accounts for 2% of all cases. Few reported malignant cases had more mitoses, increased vascularity and focal necrosis. Diagnosis of malignancy is based on increased growth rate, infiltration and metastasis.

The preoperative distinction of this tumour from other round cell tumours of infancy is essential in order to plan complete resection and therefore reducing the possibilities of tumour recurrence. Though high level of urinary excretion of VMA and serum AFP is characteristic of MNTI but it’s not always present. Because of the urgent need for surgery, laboratory testing for urinary excretion of VMA was not done in all these three cases.

The differential diagnoses for a rapidly growing mass in the maxillary area or femur for this age group includes Abscess, Haemangioma, Arterio-venous malformations, Epulis, Neuroblastoma, Rhabdomyosarcoma, Melanoma, Ewing’s sarcoma, Metastatic retinoblastoma, Lymphoma and Teratoma.

Clinical context can narrow down the differential. Non-neoplastic haemangioma and lymphangiomas have bluish discolorations and a predilection for the head and neck region in children and tend to develop rapidly within a few months after birth. Congenital Epulis is always present at birth, and can be alarmingly large and may interfere with the infant’s ability to take feed, as did the lesion reported in our case series. Congenital Epulis is almost always reported to be pedunculated whereas MNTI is usually sessile. Teratomas can be differentiated from MNTI only by histopathology by demonstrating tissues from different germ layers. Neuroblastoma is a malignant tumour occurring in infants and young children, and may arise at any site in the sympathetic nervous system, most commonly in the abdomen. Metastatic neuroblastoma occurs most commonly in the mandible, presenting clinically by the deviation of the mandible on mouth opening, periorbital ecchymosis and Horner’s syndrome, which are not seen in MNTI. Ewing’s sarcoma is a rare malignant tumour of neuroectodermal origin affecting the skeletal system, with long bones being the commonest location. It is rarely seen before the age of five years. Its occurrence in head and neck is rare and even if it occurs it is more common at mandible than maxilla. Clinically, this tumour is aggressive, characterised by rapid growth and high probability of micro-metastasis at the diagnosis. Whereas MNTI is painless, occurs in infants and most commonly located at maxilla. In the second case of our case series the lesion was present at femur for which we did an IHC marker CD99 to rule out Ewing’s sarcoma. Embryonal rhabdomyosarcoma occurs in children less than 15 years of age, clinically these tumours exhibit a fast growth reaching large dimensions and generally painless. Mostly the cases are present in the oral cavity: palate or the tongue. The patient may present with pain, paresthesia, and loss of teeth or trismus as a result of advanced tumour stage, infiltration and location. MNTI can be differentiated by its painless nature, and the most common site of occurrence is the maxilla. Oral mucosa melanomas can be differentiated from MNTI in terms of age of occurrence (fourth to seventh decades) and site i.e. palate. Endemic type of Burkitt’s lymphoma occurs in the jaws and facial bones, whereas the non-endemic type occurs at other sites. The mean age of presentation is between 7 and 14 years, whereas MMTI occurs in infants, and both the lesions can be differentiated only by histopathology.

The treatment of choice consists of complete surgical excision with lymph node dissection. The overall incidence of local recurrence is 20% within six months. Even large lesions, or those incompletely excised, can have a good prognosis, but the resection should be thorough because even 5 mm of clearance may be inadequate to prevent recurrence. Recurrence may be the consequence of incomplete removal of the primary tumour, seeding during surgery, or tumour multicentricity.

Rachidi et al. stated that the age at diagnosis is an important prognostic marker, where younger patients are more likely to develop recurrence. Based on these findings, he recommended closer monitoring of patients diagnosed within the first 2 months of life, especially all recurrences occur within 6 months from intervention.
MNTI is a benign tumour of neuroectodermal origin with rapid growth potential which makes its early diagnosis crucial to limit its expansion. However, the rarity of this tumour leads to diagnostic delay. As pointed out in this case series, a number of known pathologic entities can present at this age but confirmation of the diagnosis requires histopathological examination and IHC if necessary. No histological feature or biological marker is known to predict behaviour. Any unusual growth in infants that appear inconsistent with normal variation and reported history should be referred in time to a pathologist for assessment and diagnosis. A diagnosis of MNTI should be suspected in any tumour in an infant with round cell morphology and a careful search for large melanin containing epithelial cells will help in the accurate diagnosis. Delay in diagnoses lead to more tissue resection which in turn makes rehabilitation difficult and a costly affair.

Conflict of Interest: None.

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